Claim Objection

Claims 7-13 were objected to as depending from claim 1, but being drawn to a "method" whereas claim 1 is drawn to a "process". This objection is obviated by the cancellation of claim 7 and amendment of claims 8-13. Thus, Applicants respectfully request withdrawal of the objection to claims 7-13.

Rejection Under 35 U.S.C. §112, First Paragraph

Claims 12 and 13 were rejected under 35 U.S.C. §112, first paragraph as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains to make and/or use the invention. Applicants traverse this rejection.

The Examiner's attention is directed to MPEP § 2404 which states "biological material need not be deposited, *inter alia*, if it is known and readily available to the public or can be made or isolated without undue experimentation."

Applicants respectfully submit that the present application describes to those skilled in the art how to make and use plasmids pSJC62.3 and pBMesterase11. Page 31, line 6, to page 32, line 16 of the present application describes the construction of plasmid pBMesterase11. Plasmid pBMesterase11 is made from pJB10 and pSJC62.3 which are derived from known plasmids. Moreover, page 10, lines 14-19 of the present application state that a *A. chrysogenum* host cell transformed with plasmid pBMesterase11 identified as DC11 has been deposited with the American Type Culture Collection, Rockville, MD on January 27, 1999, under the Budapest Treaty and assigned ATCC Accession No. 74482.

Page 30, line 24 to page 31, line 4, of the present application describes the construction of plasmid pSJ62.3. The present application states that plasmid pSJ62.3 is

derived from plasmid pSJC62 described in U.S. Patent No. 5,516,679. Plasmid pJB10 is made from pSJC62 and plasmid A. Plasmid A is made from plasmid pCSN43 (described in Staben et al., 1989, Fungal Genet. Lett. 36, 79-81) and pWB19N (described in U.S. Patent No. 5,516,679). Thus, Applicants respectfully submit that the plasmids described in the present application are known and readily available to the public and the present application provides a repeatable process for obtaining plasmids pSJC62, pCSN43, pSJC62.3 and pBMesterase11. Accordingly, Applicants respectfully request withdrawal of the rejection of claims 12 and 13 under 35 U.S.C. §112, first paragraph.

Rejection under 35 U.S.C. §112, second paragraph

Claims 2-6 were rejected under 35 USC §112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The basis for this rejection is that claims 2-6 are allegedly indefinite because these claims are directed to the process of claim 1 wherein the chemical breakdown of cephalosporin C to 2-(D-4-amino-4-carboxybutyl)-thiazole-4-carboxylic acid is less than 40%, 30%, 20%, 10% and 5%, but do not recite any conditions. Applicants traverse this rejection.

Applicants respectfully submit that claims 2-6 are not indefinite. The scope of the subject matter embraced by the claims is clear. Nevertheless, the rejection of claim 2 is obviated by the cancellation of that claim. Moreover, the rejections of dependent claims 3-6 are obviated in view of the amendment of claim 1 to recite conditions wherein the temperature is about 22°C to about 29°C and the pH is about 5.5 to about 7.5 resulting in the synthesis of cephalosporin C and expression of cephalosporin esterase wherein the

cephalosporin C so produced is converted to desacetylcephalosporin C and the chemical breakdown of cephalosporin C to 2-(D-4-amino-4-carboxybutyl)-thiazole-4-carboxylic acid is less than 40%. Accordingly, Applicants respectfully request the withdrawal of the rejection of claims 2-6 under 35 USC §112, second paragraph.

Rejection under 35 U.S.C. §102(b)

Claims 1-6 and 9-11 were rejected under 35 U.S.C. §102(b) as being anticipated by Politino et al. (WO 98/12345).

The basis for this rejection is that Politino et al. (WO 98/12345) allegedly teaches a method for producing a recombinant cephalosporin esterase from *Rhodosporidium toruloides* by culturing cells of *Cephalosporin acremonium* transformed with a DNA encoding the esterase. Applicants traverse this rejection.

Applicants respectfully submit that claims 1, 3-6 and 9-11 as amended are not anticipated by Politino (WO 98/12345).

It is well–established that anticipation requires the disclosure in a single prior art reference of each element of the claim. This rejection is based on the assertion that the elements of Applicants' claimed invention are allegedly inherent in the Politino (WO 98/12345) reference.

Claim 1 as amended claims a process for the direct production of desacetylcephalosporin C comprising culturing a strain of *Acremonium chrysogenum* containing nucleic acid encoding enzymes for cephalosporin C biosynthesis and a recombinant nucleic acid encoding *Rhodosporidium* cephalosporin esterase under

conditions wherein the temperature is about 22°C to about 29°C and the pH is about 5.5 to about 7.5 resulting in the synthesis of cephalosporin C and expression of cephalosporin esterase wherein the cephalosporin C so produced is converted to desacetylcephalosporin C and the chemical breakdown of cephalosporin C to 2-(D-4-amino-4-carboxybutyl)-thiazole-4-carboxylic acid is less than 40%. Politino does not disclose a process for the direct production of desacetylcephalosporin C wherein the processs is carried out at a temperature of from about 22°C to about 29°C and the pH is about 5.5 to about 7.5 wherein the chemical breakdown of cephalosporin C to 2-(D-4-amino-4-carboxybutyl)-thiazole-4-carboxylic acid is less than 40%. Thus, Politino does not disclose all elements of the claims.

"In relying upon the theory of inherency, the Examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art." Ex parte Levy, 17 USPQ2d, 1461, 1464 (Bd. Pat. App. & Inter. 1990) (emphasis in original).

As stated by the Federal Circuit:

> To serve as an anticipation when the reference is silent about the asserted inherent characteristic, such gap in the reference may be filled with recourse to extrinsic evidence. Such evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill.

Continental Can Co. USA v. Monsanto Co., 948 F.2d 1264, 1268, 20 USPQ 2d 1746, 1749 (Fed. Cir. 1991). The CCPA has stated that "[i]nherency ... may not be established by probabilities or possibilities. The mere fact that a certain thing *may* result from a given set

of circumstances is not sufficient." In re Oelrich, 666 F.2d 578, 581, 212 USPQ 323, 326 (C.C.P.A. 1981). That is, the missing element or function must necessarily result from the prior art reference. See also the M.P.E.P., which states at §706.02 that "[a]ny feature not directly taught must be inherently present."

Neither a basis in fact, nor technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art has been provided. Evidence must establish both that (*i*) the missing descriptive matter is *necessarily present* in the thing described in the reference and (*ii*) it would be so recognized by persons of ordinary skill in the art. See also Electro Medical Systems S.A. v. Cooper Life Sciences Inc., 34 F.3d 1048, 1052, 32 USPQ2d 1017, 1020 (Fed. Cir. 1994) (one asserting an inherent anticipation is required to show that this fact would be recognized by persons of ordinary skill).

All of the elements of Applicants' claimed invention are not present in the Politino (WO 98/12345).

Therefore, Applicants respectfully request withdrawal of the rejection of claims 1-6 and 9-11 under 35 U.S.C. 102(b).

Claims 1-6 and 9-11 were rejected under 35 U.S.C. §102(e) as being anticipated by Politino et al. (U.S. Patent No. 5,869,309). Applicants traverse this rejection.

For the reasons discussed above, Applicants' claimed invention is not anticipated by U.S. Patent No. 5,869,309.

Claim 1 as amended claims a process for the direct production of desacetylcephalosporin C comprising culturing a strain of *Acremonium chrysogenum* containing nucleic acid encoding enzymes for cephalosporin C biosynthesis and a recombinant nucleic acid encoding *Rhodosporidium* cephalosporin esterase under

conditions wherein the temperature is about 22°C to about 29°C and the pH is about 5.5 to about 7.5 resulting in the synthesis of cephalosporin C and expression of cephalosporin esterase wherein the cephalosporin C so produced is converted to desacetylcephalosporin C and the chemical breakdown of cephalosporin C to 2-(D-4-amino-4-carboxybutyl)-thiazole-4-carboxylic acid is less than 40%. Politino does not disclose all elements of the claims.

The Office Action does not point to any evidence that (*i*) the descriptive matter missing in U.S. Patent No. 5,869,309 is *necessarily present* in the methods described in that reference and (*ii*) it would be so recognized by persons of ordinary skill in the art.

Thus, Applicants respectfully request the withdrawal of the rejection of claims 1-6 and 9-11 under 35 U.S.C. §102(e).

Claims 7 and 8 were rejected under 35 U.S.C. § 103(a) as being unpatentable over any of Politino et al. alone or in view of Smith et al. It is not clear from the Office Action which Politino et al. reference is being cited in this rejection. Applicants request that the Examiner clarify whether this rejection is referring to both Politino references or one of the Politino references. Nevertheless, Applicants traverse this rejection.

Neither Politino (WO 98/12345 or 5,869,309) nor Smith, alone or in combination, disclose Applicants' claimed invention. For the reasons discussed above, neither Politino reference discloses Applicants' claimed invention. Smith merely discloses a process for the preparation of desacetyl cephalosporin C which comprises fermenting a cephalosporin C producing microorganism in the presence of an amount of an acetylesterase enzyme. Smith merely suggests temperature and pH conditions for culturing the cephalosporin C producing microorganism in the present of an acetylesterase enzyme. Smith does not

disclose or suggest conditions for culturing *Acremonium chrysogenum* containing (1) a nucleic acid encoding enzymes for cephalosporin C biosynthesis and (2) a recombinant nucleic acid encoding *Rhodosporidium* cephalosporin esterase. Obvious to try is not obviousness. Given the disclosures of Politino and Smith, it would not have been obvious to one of ordinary skill in the art to carry out Applicants' claimed process for the direct production of desacetylcephalosporin C.

Nowhere do Politino or Smith disclose Applicants' claimed process for the direct production of desacetylcephalosporin C comprising culturing a strain of *Acremonium chrysogenum* containing nucleic acid encoding enzymes for cephalosporin C biosynthesis and a recombinant nucleic acid encoding *Rhodosporidium* cephalosporin esterase under conditions wherein the temperature is about 22°C to about 29°C and the pH is about 5.5 to about 7.5 resulting in the synthesis of cephalosporin C and expression of cephalosporin esterase wherein the cephalosporin C so produced is converted to desacetylcephalosporin C and the chemical breakdown of cephalosporin C to 2-(D-4-amino-4-carboxybutyl)-thiazole-4-carboxylic acid is less than 40%. Likewise, the combination of Politino and Smith does not disclose a process for the direct production of desacetylcephalosporin C comprising culturing a strain of *Acremonium chrysogenum* containing nucleic acid encoding enzymes for cephalosporin C biosynthesis and a recombinant nucleic acid encoding *Rhodosporidium* cephalosporin esterase at a temperature of about 25°C to about 29°C and a pH of about 6.2 to about 7.0, during the vegetative cell growth phase; and at a temperature of about 22°C to about 26°C and a pH of about 5.7 to about 6.5 during the desacetylcephalosporin C production phase. The combination of Smith and Politino does not provide Applicants claimed invention.

Thus, it would not have been obvious to one of ordinary skill in the art at the time the invention was made to carry out Applicants' claimed process for the direct production of desacetylcephalosporin C. Accordingly, Applicants respectfully request the withdrawal of the rejection of claims 7 and 8 under 35 U.S.C. § 103(a).

The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment, to Account No. 19-3880 in the name of Bristol-Myers Squibb Company.

CONCLUSION

In view of the preceding remarks, reconsideration of this application and its allowance are respectfully requested. If the Examiner wishes to discuss this reply or any aspect of this case, she is invited to contact the undersigned attorney.

Respectfully submitted,

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Date: February 10, 2003

Version with Markings to Show Changes Made

IN THE SPECIFICATION:

IN THE CLAIMS:

1. A process for the direct production of desacetylcephalosporin C comprising culturing a strain of *Acremonium chrysogenum* containing nucleic acid encoding enzymes for cephalosporin C biosynthesis and a recombinant nucleic acid encoding *Rhodosporidium* cephalosporin esterase under conditions wherein the temperature is about 22°C to about 29°C and the pH is about 5.5 to about 7.5 resulting in the synthesis of cephalosporin C and expression of cephalosporin esterase wherein the cephalosporin C so produced is converted to desacetylcephalosporin C and the chemical breakdown of cephalosporin C to 2-(D-4-amino-4-carboxybutyl)-thiazole-4-carboxylic acid is less than 40%.

8. The [method] process of Claim 1 carried out at a temperature of about 25°C to about 29°C and a pH of about 6.2 to about 7.0, during the vegetative cell growth phase; at a temperature of about 22°C to about 26°C and a pH of about 5.7 to about 6.5 during the desacetylcephalosporin C production phase.

9. The [method] process of Claim 1 wherein the recombinant nucleic acid encoding *Rhodosporidium* cephalosporin esterase is DNA.

10. The [method] process of Claim 1 wherein the recombinant nucleic acid encoding *Rhodosporidium* cephalosporin esterase is DNA and a part of a plasmid.

11. The [method] process of Claim 10 wherein the recombinant nucleic acid encoding *Rhodosporidium* cephalosporin esterase has the sequence of SEQ[.] ID[.] No[.]:1 or 3.

12. The [method] process of Claim 10 wherein the plasmid is pSJC62.3.

13. The [method] process of Claim 10 wherein the plasmid is pBMesterase11.